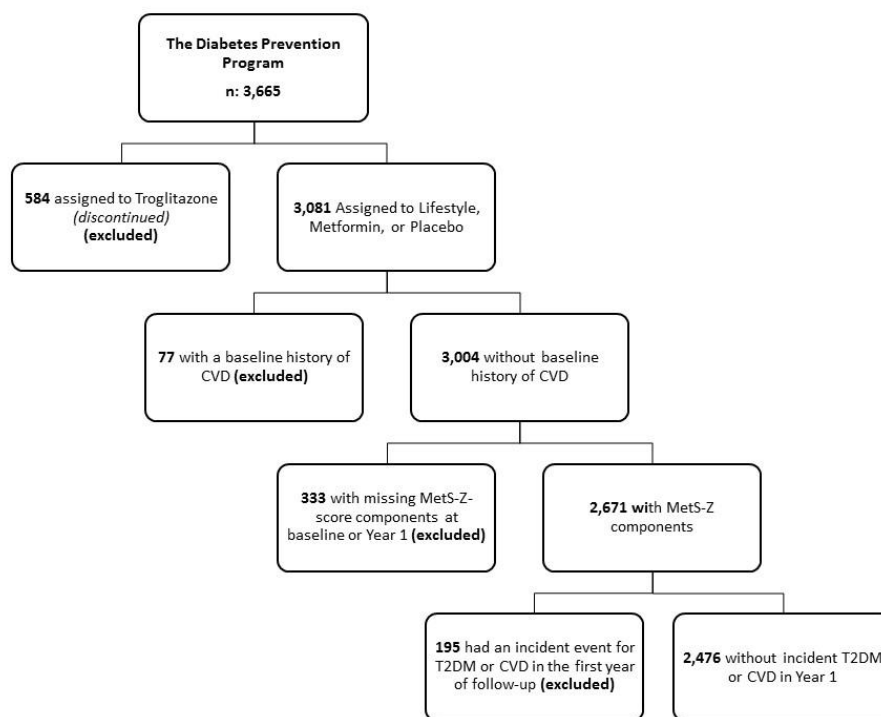


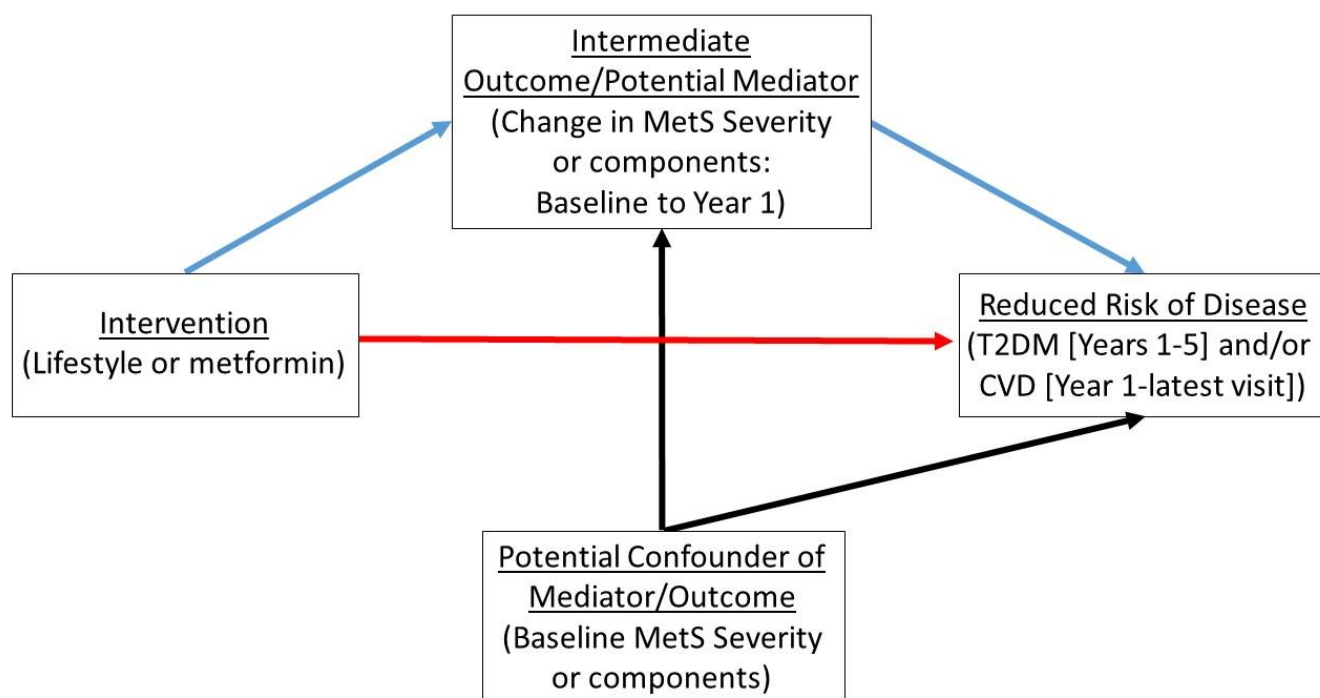
## SUPPLEMENTARY DATA

**Supplementary Figure S1.** Flow diagram of DPP participants included and excluded in the analysis.



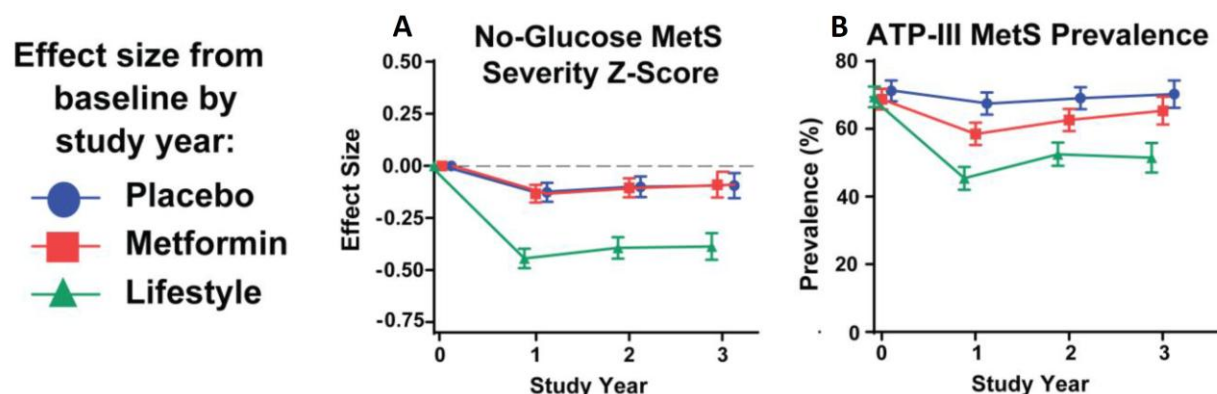
## SUPPLEMENTARY DATA

**Supplementary Figure S2.** Conceptual diagram of mediation analysis. We assessed for changes in the MetS-severity Z-score and the individual MetS outcomes as intermediate outcomes that may represent means by which the randomized interventions exerted their effects on the outcomes of incident T2DM and T2DM with later CVD. The red line portrays the total direct effect (TDE), or the effect of the intervention on reduced risk of disease not accounted for by the intermediate outcome. The blue lines represent the pure indirect effect (PIE), or the effect of the intervention on reduced risk of disease through the intermediate outcome, which is also related to baseline values (black lines). The total effect thus = TDE + PIE.



## SUPPLEMENTARY DATA

**Supplementary Figure S3.** Changes in a glucose-free MetS-severity Z-score and ATP-III MetS prevalence during 3 years of intervention. Temporal changes are shown during intervention with lifestyle modification, metformin and placebo, including A) mean effect size (+/- 95% confidence interval) for a MetS-severity Z score formulated without glucose as a component (No-glucose MetS-Z) and B) prevalence of ATP-III MetS. In A) the data points for metformin and placebo are nearly interchangeable. Mean absolute effects are provided in Supplementary Table 1.



# SUPPLEMENTARY DATA

**Supplementary Table 1.** Actual Changes from Baseline Values (Mean  $\pm$  SD) of MetS and its components by study year and treatment group

		Baseline Value	Year 1 Change from Baseline	Year 2 Change from Baseline	Year 3 Change from Baseline
Placebo					
MetS-Z		0.81 $\pm$ 0.62	-0.08 $\pm$ 0.44	-0.0 $\pm$ 0.5	-0.01 $\pm$ 0.5
MetS-Z (no glucose)		0.57 $\pm$ 0.68	-0.08 $\pm$ 0.43	-0.1 $\pm$ 0.5	-0.1 $\pm$ 0.5
Waist Circumference (cm)		105.2 $\pm$ 14.0	-0.9 $\pm$ 5.6	-0.9 $\pm$ 6.5	-0.8 $\pm$ 6.6
SBP (mmHg)		123.3 $\pm$ 14.2	-1.1 $\pm$ 12.8	-0.2 $\pm$ 13.3	-0.3 $\pm$ 14.0
Glucose (mg/dL)		106.6 $\pm$ 7.1	-0.8 $\pm$ 12.0	1.4 $\pm$ 10.6	2.5 $\pm$ 14.6
HDL (mg/dL)		45.0 $\pm$ 11.6	0.0 $\pm$ 6.0	-0.5 $\pm$ 6.6	-0.1 $\pm$ 7.0
Triglycerides (mg/dL)		168.2 $\pm$ 94.5	-10.0 $\pm$ 73.3	-10.6 $\pm$ 78.5	-10.1 $\pm$ 80.9
Metformin					
MetS-Z		0.74 $\pm$ 0.65	-0.18 $\pm$ 0.44	-0.10 $\pm$ 0.5	-0.08 $\pm$ 0.5
MetS-Z (no glucose)		0.55 $\pm$ 0.68	-0.09 $\pm$ 0.42	-0.1 $\pm$ 0.4	-0.07 $\pm$ 0.5
Waist Circumference (cm)		105.3 $\pm$ 14.3	-2.3 $\pm$ 6.0	-2.0 $\pm$ 6.6	-1.4 $\pm$ 6.7
SBP (mmHg)		124.1 $\pm$ 14.7	-1.1 $\pm$ 13.7	-1.1 $\pm$ 13.7	-0.9 $\pm$ 13.6
Glucose (mg/dL)		106.8 $\pm$ 7.5	-4.8 $\pm$ 10.3	-1.6 $\pm$ 10.7	-0.9 $\pm$ 12.2
HDL (mg/dL)		46.3 $\pm$ 11.7	0.8 $\pm$ 6.5	-0.1 $\pm$ 7.1	0.2 $\pm$ 7.5
Triglycerides (mg/dL)		157.1 $\pm$ 88.1	-5.1 $\pm$ 67.5	-6.1 $\pm$ 70.4	-5.6 $\pm$ 74.8
Lifestyle					
MetS-Z		0.77 $\pm$ 0.64	-0.40 $\pm$ 0.50	-0.31 $\pm$ 0.53	-0.27 $\pm$ 0.57
MetS-Z (no glucose)		0.58 $\pm$ 0.68	-0.30 $\pm$ 0.47	-0.27 $\pm$ 0.51	-0.26 $\pm$ 0.50
Waist Circumference (cm)		105.4 $\pm$ 14.9	-6.6 $\pm$ 7.3	-5.9 $\pm$ 7.4	-5.2 $\pm$ 7.7
SBP (mmHg)		123.6 $\pm$ 14.6	-3.3 $\pm$ 13.5	-3.5 $\pm$ 13.1	-2.9 $\pm$ 14.6
Glucose (mg/dL)		106.5 $\pm$ 7.2	-5.6 $\pm$ 10.3	-2.4 $\pm$ 10.9	-0.9 $\pm$ 12.8
HDL (mg/dL)		46.7 $\pm$ 12.6	1.1 $\pm$ 7.2	0.7 $\pm$ 7.4	0.9 $\pm$ 7.4
Triglycerides (mg/dL)		161.9 $\pm$ 98.2	-26.0 $\pm$ 71.5	-23.4 $\pm$ 72.6	-26.8 $\pm$ 74.0

Abbreviations: MetS-Z = metabolic syndrome severity Z-score, HDL = high density lipoprotein cholesterol, TRI = fasting triglycerides, SBP = systolic blood pressure.